




# Mammalian Secreted Phospholipases A2 and Their Pathophysiological Significance in Inflammatory Diseases

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## Abstract:

Phospholipases A2 (PLA2s) represent a growing family of enzymes that catalyze the hydrolysis of phospholipids at the sn-2 position leading to the generation of free fatty acids and lysophospholipids. Mammalian PLA2s are divided into two major classes according to their molecular mass and location: intracellular PLA2 and secreted PLA2 (sPLA2). Type-IIA sPLA2 (sPLA2-IIA), the best studied enzyme of sPLA2, plays a role in the pathogenesis of various inflammatory diseases. Conversely, sPLA2-IIA can exert beneficial action in the context of infectious diseases since recent studies have shown that this enzyme exhibits potent bactericidal effects. Induction of the synthesis of sPLA2-IIA is generally initiated by endotoxin and a limited number of cytokines via paracrine and / or autocrine processes. If the mechanisms involved in the regulation of sPLA2-IIA gene expression have been relatively clarified, little is known on the mechanisms that regulate the expression of other sPLA2. There have been substantial progresses in understanding the transcriptional regulation of sPLA2-IIA expression. Recently, transcription factors including NF- $\kappa$ B, PPAR, C / EBP have been identified to play a prominent role in the regulation of sPLA2-IIA gene expression. The activation of these transcription factors is under the control of distinct signaling pathways (PKC, cAMP ...). Accumulating evidences in the literature suggest that cytosolic PLA2 together with two sPLA2 isozymes (sPLA2-IIA and sPLA2-V) are functionally coupled with cyclooxygenase-1 and 2 pathways, respectively, for immediate and delayed PG biosynthesis. This spatio-temporal coupling of cyclooxygenase enzymes with PLA2s may represent a key mechanism in the propagation of inflammatory reaction. Unraveling the mechanisms involved in the regulation of the expression of sPLA2s is important for understanding their pathophysiological roles in inflammatory diseases.

**Keywords:** Phospholipases; cyclooxygenase; lipoxygenase; Protein Kinases; Glucocorticoids; Dexamethasone; Transforming growth factor; Platelet-Derived Growth Factor (PDGF); Insulin like growth factor-1 (IGF-1); sPLA2 RECEPTORS

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### **Group IIA Phospholipase A2 Mediates Lung Injury in Intestinal Ischemia-Reperfusion.**

Annals of Surgery. 232(1):90-97, July 2000.

*Koike, Kaoru MD, PhD \*; Yamamoto, Yasuhiro MD, PhD \*; Hori, Yozo PhD +; Ono, Takashi PhD +*

#### **Abstract:**

**Objective:** To assess the mechanistic role of group IIA phospholipase A2 (PLA2) in the process of local and distant organ injury after intestinal ischemia-reperfusion.

**Summary Background Data:** Intestinal ischemia-reperfusion produces lung injury by a mechanism that involves PLA2 activation, but it is unclear which isozyme is responsible for this phenomenon. Group IIA PLA2, one of the secreted forms of PLA2, is known to play a pivotal role in a variety of inflammatory reactions.

**Methods:** Rats underwent 45 minutes of superior mesenteric artery occlusion in the presence and absence of pretreatment with group IIA PLA2 inhibitor, S-5920/LY315920Na (20 mg/kg, subcutaneously, 30 minutes before clamping). At 2 hours of reperfusion, intestinal and lung leak was assessed by 125I-albumin tissue/blood ratio, and liver injury was estimated by serum alanine aminotransferase. PLA2 activities in tissues and sera were quantitated by phosphatidyl-glycerol/sodium cholate mixed micelle assay. PLA2 activities in tissues were also measured after in vitro preincubation with EDTA, S-5920/LY315920Na, or antirat group IIA PLA2 antibody.

**Results:** Intestinal ischemia-reperfusion provoked intestinal leak, liver injury, and lung leak, whereas tissue PLA2 activity was decreased in the intestine, unchanged in the liver, and increased in the lung. Serum PLA2 activities were increased in the portal and systemic circulation during ischemia. Pretreatment with S-5920/LY315920Na eliminated PLA2 activities in all tissues and sera and only abolished lung leak. The in vitro experiment revealed that most of the intestinal and lung PLA2 activities were inhibited by EDTA, S-5920/LY315920Na, and antirat group IIA PLA2 antibody, but hepatic PLA2 activity was not.

**Conclusion:** Intestinal ischemia-reperfusion appears to produce lung injury by a mechanism that involves group IIA PLA2 activation. Intestinal ischemia-reperfusion is likely to promote intestinal and hepatic injury independent of group IIA PLA2.

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### ATTENUATION OF ISCHEMIA AND REPERFUSION INJURY OF CANINE LIVERS BY INHIBITION OF TYPE II PHOSPHOLIPASE A2 WITH LY3297221.

Transplantation. 71(8):1040-1046, April 27, 2001.

Ogata, Kenji 2; Bong Jin, Maeng 2; Taniguchi, Masahiko 2; Suzuki, Tomomi 2; Shimamura, Tsuyoshi 2; Kitagawa, Norihiko 2; Magata, Shinichiro 2; Fukai, Moto 2; Ishikawa, Hiroto 2; Ono, Takashi 4; Furukawa, Hiroyuki 2; Fujita, Miri 3; Todo, Satoru 2,5

#### Abstract:

**Background.** Membrane phospholipid breakdown, caused by ischemia and reperfusion (I/R) of the liver, releases free fatty acids including arachidonic acids and lysophospholipids, which serve as precursors of various inflammatory lipid derivatives. Phospholipase A2 (PLA2) is a key enzyme that initiates this reaction. In this study, we tested our hypothesis that a type II PLA2 inhibitor, LY329722, could attenuate hepatic I/R injury caused by a 2-hr total hepatic vascular exclusion (THVE) in dogs.

**Methods.** Eighteen beagle dogs, subjected to a 2-hr THVE, were divided into three groups. Group 1 (n=6) was untreated and served as a control group. LY329722 was administered to animals in group 2 (n=6) intravenously (0.2 mg[middle dot]kg<sup>-1</sup>[middle dot]hr<sup>-1</sup>) for 60 min before ischemia, and to animals in group 3 (n=6) for 60 min starting 15 min before reperfusion (0.2 mg[middle dot]kg<sup>-1</sup>[middle dot]hr<sup>-1</sup>). Animal survival, systemic and splanchnic hemodynamics, hepatic tissue blood flow, liver functions, energy metabolism, hepatic venous thromboxane B2 and endothelin-1 levels, phospholipid levels and tumor necrosis factor-[alpha] mRNA expression in liver tissue, and histopathologic findings were evaluated.

**Results.** Two-week animal survival was 33% (two of six) in group 1, and 100% (six of six) in groups 2 and 3. LY329722 improved systemic and splanchnic hemodynamics, hepatic tissue blood flow, and energy metabolism, reduced liver enzyme, thromboxane B2, and endothelin-1 release, prevented hepatic phospholipid degradation and tumor necrosis factor-[alpha] mRNA expression, and lessened histopathologic damage and the number of neutrophil infiltrating into the liver tissue.

**Conclusion.** The present study demonstrated that a type II PLA2 inhibitor, LY329722, attenuated hepatic I/R injury caused by a 2-hr THVE model in dogs.

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